drawn-out war with activity on many fronts. When treatment is started it must be based on strategic plans to suit the patient for a duration of at least five years, and maybe for a long lifetime. The plan must be to stifle and eradicate the infection while preserving at a maximum the function of the diseased part. Extensions of the disease and complications in other parts of the lungs and other parts of the body must be dealt with quickly and as fully as possible. It is necessary to be in a position to change, modify, enlarge, combine, or stop the methods of treatment in use (if necessary and if possible) at any time, to meet new situations. Pneumothorax is the most flexible and versatile method of collapse therapy that can be applied. It can be lessened, enlarged, shifted from side to side, applied to both sides, combined with any other form of treatment — rest, drug, antimicrobic, or surgical — or stopped at will. It can sometimes be stopped and restarted with surprising effectiveness. A treatment which has had such long and widespread effective usage, the value and limitations of which have been determined, is not one to be dropped. Rather, it is one to be preserved and utilized in better refinements of application so as to avoid abuses. It is to be used in its greatest effectiveness in combination with all other forms of treatment, with no undue claims made for accomplishments with it alone. As progress is made in methods to prevent tuberculosis and to diagnose and treat it early when it does occur, the goal is minimum sacrifice of tissue or function. Progress toward that goal will eventually reduce the need for the clumsy methods of collapse and resection which now must be used; and the last of these methods to be abandoned will be the flexible, versatile pneumothorax, narrowed more and more in its application but effective to the last well chosen case.

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The Pathogenesis of Tuberculosis as an Ebb-and-Flow Struggle Between Two Variable Antagonists

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THE pathogenesis of tuberculosis has become clarified over the last few decades so that we now may view the struggle between the host and the parasite as we would any contest where the stakes are survival of one or the other of the antagonists. Until recent times, however, knowledge was meager. Little by little, men like Bayle and Laennec parted the curtains on some of the elementary features of the tuberculous process.

Bayle was first to describe the miliary tubercle as a small "gray granulation." Laennec observed that many miliary tubercles had soft yellow centers and that they seemed to become larger as they became older. He reasoned that Bayle's hard gray granulations were merely the "green fruit" while the yellow miliary tubercles were the "ripe fruit." This is probably the only error committed by the immortal Laennec. He was not wrong, however, in his contention that all forms of tuberculosis were due to one cause. Too much tribute cannot be paid to his keenness of insight into the pathologic character of the disease. With much more information at hand a half century later, Virchow tried to tear down Laennec's unity theory, but only confused the scientific world for a time by his fallacious "dualism," a doctrine proclaiming that tuberculosis was a dual process of inflammatory phthisis and the tumorous tuberculosis. As a result of the enthusiasm for this contention Niemeyer made the preposterous statement that the worst thing that could happen to a phthisical patient was to become tuberculous. Virchow's influence held great sway throughout the latter part of the century. Fragmentary knowledge was added, such as that of Küster's epithelioid tubercle, Langerhans' giant cells, Reinhardt's caseous pneumonia and Weigert's intravenous tubercles. Parrot and later Küss laid the groundwork for the present understanding of primary tuberculous infection. These observations were made before the discovery of the tubercle bacillus; afterward in rapid sequence came the works of H. Albrecht, E. Albrecht, Ghon, Ranke and others, amplifying Parrot's pioneer studies. Since then dozens of names have been added to the list of investigators, and many theories have been proposed.

It is the desire of the author here to by-pass much that has been written and go directly to the most fundamental aspects of pathology and pathogenesis of tuberculosis. This will involve a consideration first of the host, secondly of the bacillus, then of the two in active encounter with each other, followed by a discussion of the resultant forms the disease may assume.

In few if any other diseases do we meet such a variable pattern as presents itself in tuberculosis. The process may be infinitesimal, one of limited involvement that heals promptly; or it may be over-

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whelming and rapidly fatal, depending on a multitude of factors, including age, sex, and race of the host, and type, nature, virulence and dosage of the bacilli. There may be an "ebb and flow" due to many "accidents" as proclaimed by Krause, who stated that "in the last analysis clinical tuberculosis is the fruition of numerous accidental circumstances." Trauma, a debauch, an illness, fatigue, mental anxiety—any of these may upset the delicate equilibrium between healing and progression. On the other hand, the development of special features of the bacillus may also lead to a breakthrough of the host's defenses and spread of the disease.

Let us visualize first the recently infected host. The infection runs its course, producing the well known acute inflammation, followed on the one hand by gradual recession and healing, or, on the other, by varying degrees of progression. In the healing process suffice it to say that humoral and cellular elements isolate the bacilli, encapsulate them, and ultimately destroy them in the caseous and calcified tubercle.

Before the interruption of this healing mechanism is discussed more at length, it must be noted that bacilli entering a previously so-called "virgin soil" have less inhibition than those entering a previously infected host; Krause,[6, 7] Willis,[20] Smithburn,[14] Sabin[12] and others demonstrated this point in animals. These investigators found that there is a prompt spread of bacilli by the lymphatics to the bloodstream and throughout the body. If in such cases the numbers of bacilli are great, the result may be a fatal generalized infection. Usually the generalization is slight and most of the bacilli are carried to distant tissue where they are destroyed.

The lesions at the local site and in the adjacent lymph nodes, however, go through an evolutionary development, involving the formation of a nebulous infiltrate, followed by encapsulation. The tissue cells begin to develop a sensitivity to the many proteins elaborated by the bacillus, especially to tuberculin. The cells are injured by the newly forming toxins and many of them die. Necrosis sets in, the cells in the center of the process caseate and disintegrate, and a wall of modified monocytes (epithelioid cells) gathers around the outside of the central caseous mass. These epithelioid cells may form a primitive capsule to wall off the central core of bacilli, or the caseation may spread, depending on the quantitative amount of sensitiveness, or "allergy," as it was originally called by Pirquet, and the other factors previously mentioned.

There is at about this time another change in the cellular response, also associated with the amount of hypersensitiveness. Along with the monocytes and other cells present in the early process, polymorphonuclear cells begin to appear in greater number. The result is more liquefaction and more caseation. There is a complex relationship between the factors of sensitivity, immunity, and rate of healing. In general it may be stated that the disease process will probably remain benign if healing of the lesions has progressed sufficiently and if sufficient immune factors have appeared before the appearance of an overwhelming allergic reaction or other deleterious factors.

It is conceivable and probably true that there are great differences in various infected areas; in one place healing may be taking place and in another rapid caseation may occur. If such rapid caseation happens to progress through the wall of a pulmonary vein, through the capsule of a lymph node into a bronchus, into the pleural cavity, into lung tissue, or even through the capsule of a newly formed tubercle, a rapidly forming process may result. In some instances bacilli pour through these "flood gates" to produce fatal disease. It is the suddenness and extent of these accidents that lead to their seriousness. The body is not prepared to meet such a catastrophe, the result being an overwhelming allergic response with widespread inflammation.

In infants and young adults the tendency for softening to occur around the tubercles seems to be more prevalent than in other age groups. There are growth factors and perhaps other anatomic-physiologic complexes that limit the fibrosis in the primary tubercles and as a result there may be a greater tendency toward liquefaction permitting the walls of newly formed tubercules to break more readily. Instead of becoming healed foci, the tubercles are prone to develop as small ulcers from which extension of the disease may take place. Thus the age of the host plays an important role in determining the character of the infection and, sometimes, the outcome of the disease process.

The same reasoning may be applied to other differences in the host—differences in sex, race, state of nutrition, and in the presence or absence of associated diseases. Frequently a complex of unfavorable factors acts to accelerate the disease process.

Now to a consideration of the parasite—the tubercle bacillus. Although there are probably almost as many variables in the parasite as in the host, they are not easy to detect and must usually be determined by indirect evidence.

One of the most striking features of the tubercle bacillus is it ubiquity. The bacilli or closely related forms exist as parasites in nearly all animal species. Insofar as man is concerned, there are only three important types—the avian, bovine and human. The avian differs widely from the human strain but the bovine is so similar that some investigators believe the one evolved directly from the other and would class the two together as mammalian. Within the human strain alone, however, there are wide variations in virulence, morphologic factors, and biological characteristics, all of which may be reflected in the effects on the host.

In studying morphologic delineations, Koch observed granules resembling spores, but he quite properly attached only academic importance to them. Metchnikoff noted branching; Spengler noted dispersions of nuclear material in fine granules; Much described four kinds of non-acid-fast forms

found principally in old and healing lesions; Arloing,[1] Vaudremer,[19] Valtis,[18] Ferran[2] and others described rapid-growing non-acid-fast variants; Mellon,[8, 9] and Kahn[5] described what they thought were life cycles.

This whole array of extraordinary phenomena, including others not mentioned, is too extensive to be passed over as of no importance. There is surely some meaning to all these variations from what seemed to be the prevalent or common manifestations of the tubercle bacillus. To one who has worked only with cultures of the bacilli the validity of many of the observations might be questionable. However, working over a span of years with all kinds of pathological material, the author has come to believe in practically all the observations reported, although not necessarily in the interpretation of the phenomena. Furthermore, the author has made some pertinent observations, some of which will be described here.

First, with regard to granules, the author has observed within tubercle bacilli granules ranging in size from huge central spore-like bodies to smaller bipolar bodies on down to innumerable nuclear acmulations along the bodies of the bacilli.[16] These observations have been confirmed by others using the electron microscope. The significance of the phenomena is an unsolved problem; whether these nuclear accumulations are an atavistic tendency to form spores or are part of a life cycle or something else, is still unknown. However, it would be logical to suppose that since the tubercle bacillus is probably, biologically and geologically, a recent adaptation from the plant world, the phenomenon of granules is an atavism of spore formation. It may be due to a reversion occurring occasionally in the normal development of the parasite or it may be a response due to the pressure of an unfavorable environment.

In addition to observing these granules, the author carried out studies to try to solve their meaning. By treating the material from animal or human organs in different cultural environments and watching the results under the dark-field microscope, and by making special stains at intervals, the granules were found to elongate directly, bud, or enlarge into doughnut shapes which, on opening, formed horseshoe shapes and, ultimately, straight bacilli. An interesting feature of this phenomenon was that it was observed with practically all sizes of granules. On one occasion recently this phenomenon was observed in material aspirated from the bronchus of a child.

It may be stated, probably as an axiom, that a truly ideal environment for growth of the tubercle bacillus does not exist. It is known that under certain experimental conditions a certain rather constant result can be obtained. There are variations, however, even within all of these ideal conditions, as all who have worked with H37 and BCG can testify. But it is a far cry from this "most ideal" environment to all the situations which different strains of tubercle bacilli encounter in the living body. As the author has stated in earlier writings, it is the difference between a pugilist shadow-boxing and one actually fighting an opponent. All the weak points of growth are tested in the many animal species, in the many organs of the different species with their great growth-producing differences, and in the individual cases where there may be rapid spread of the disease, a slow healing, or a back-and-forth struggle as the host and parasite contend for advantage.

This raises the question of the biological optimum size of the tubercle bacillus. A size of 0.5 to 0.7 micron in diameter by 2 to 10 microns in length seems under usual conditions to allow optimum absorption of nourishment, and ideal resistance to deleterious factors, thus providing conditions for the best possible growth. Under favorable conditions in culture and animal host, then, the bacilli are normally found within that size range. In other circumstances the bacilli may vary and occasionally develop granules of varying size from those barely visible under the usual magnification to oversized and ill-shaped forms.

Another observation made by the author is with regard to the regeneration of some of the granules into normal bacilli. In one instance, using the Peterfie method, a single large granule was selected and from it was grown a culture that produced ordinary tubercle bacilli. Also, in smears of growing cultures, small microcolonies of acid-fast granules appeared. Stains made at later intervals revealed the emergence from these microcolonies of small bacilli, at first extremely minute but later assuming a normal size. This observation was made only twice, but it was so striking that the author believes it is what Spengler saw in his "splitter" forms.

Another variation of the tubercle bacillus pertains to its staining qualities. Anyone following the growth on liquid media has noticed how the fresh "skin" that grows out is at first non-acid-fast and how, as the culture ages, the bacilli gradually take on acid fastness. Arloing, Ferran and others claimed to have "captured" some of these rapidly growing forms and kept them growing as non-acid-fast forms or weakly acid-fast forms. This observation, difficult to prove, seems biologically possible.

In the author's work, it was observed at one time that certain of the huge granules referred to developed into non-acid-fast, non-virulent tetrads. The reason for feeling that these were degenerate forms was that there was a gradual disappearance of the acid fastness of the parent granules as the tetrads formed.

The phenomena just described seem to support the idea that degenerate forms may emanate from tubercle bacilli under certain of the innumerable environmental conditions possible within the animal host. As an idea to think about along this line, the causes of sarcoidosis, Poncet's rheumatism, and some acute non-specific phases of tuberculosis might possibly be attributed to one of these variants that

has lost the characteristics of the tubercle bacillus and yet is able to produce disease in a suitable host or aggravate an existing disease process.

There are also changes of virulence and appearance produced by the specialized environment of certain body tissues. Griffith's[4] work on bacilli recovered from skin lesions has borne out the fact that practically all tubercle bacilli obtained from these lesions are atypical; about a third cannot be classified as human, bovine, or avian. It is a well known fact that bone and gland lesions frequently harbor a different type of bacillus than is obtained from ordinary lesions. Likewise genito-urinary lesions produce bacilli that tend to grow differently and are more prone to produce generalized disease and meningitis.

Another aspect of the germ should be mentioned, that of gross colony morphology and the differences in virulence manifested by the rough- and smooth-growing forms. Practically every strain of tubercle bacillus has been broken down into rough and smooth variants.

Another feature is chromogenesis. It is difficult to prove that chromogenesis develops in tubercle bacilli but it is equally difficult to prove that some of the chromogens are not variants of tubercle bacilli. It has commonly been observed that typical-appearing colonies of bacilli grown from sputum will turn yellow or orange in old cultures or only after exposure to oxygen. Pinner[10] passed many of these forms through animals and found a few strains were considerably virulent.

Finally, there is unequivocal proof of biological variations of tubercle bacilli in acquiring resistance to antibiotic and chemical drugs. Especially is this true of response to streptomycin. A striking feature is the wide variation of resistance in different strains of bacilli. The suppressive effect on the tubercle bacilli of the various drugs has not been entirely explored, but when such unfavorable effects are brought to bear, it can be expected that many signs of bacterial deterioration and degradation will be found. One of these appears to be an increase in chromogenesis — with and without virulence.

The two antagonists have now been introduced, with an indication of their respective strengths and weaknesses. In actual combat there is an interplay of the many factors known and perhaps of an even greater number still unknown.

In the disease process many individual bacilli or strains of bacilli are destroyed, with local or general healing; others acquire resistance and become more virulent, with exacerbation of the disease. The host may develop a high sensitivity locally or generally, allowing a break in the line of defense. Hosts of varying age, race, sex and under innumerable environmental conditions are in combat with a variable parasite. In addition, the factor of dosage of bacilli plays a vital role. The result is protean tuberculosis with all its ebb and flow from healing on the one hand to death on the other.

As a means of understanding better this whole struggle, it is helpful to group the various factors of host and parasite at two extremes of a chart. On one side are arranged all the favorable factors for a cure of the disease in the host, and on the other are the unfavorable factors which favor a progression of the disease. The "ideal" host would be a male of a resistant race, in the prime of life, in good health, and in pleasant environment of living and working conditions. The "ideal" parasite, from the standpoint of the host, would be one of the less virulent strains of bacilli, in small dosage, and susceptible to the many environmental factors. The disease which results from the combination of these two groups may be put on the left side of the chart, where also are listed the types of benign and healing disease that have been described in the past. For example, Bayle's gray granulations probably result from a scattering of bacilli of relatively low virulence within a resistant host having a "favorable" type of allergy. The nodular lesions called Simon[13] foci are those arising from a few clusters of bacilli, but having produced a rather large fibrocaseous, hematogenous type of lesion. The foci of Puhl,[11] Stefko,[15] Ghon[3] and others represent nodular lesions that have undergone varying degrees of healing. Many lesions formerly described by different workers are therefore the same, except for a different age pattern. Any fibroid or calcified lesion indicates age.[17] There are morphological characteristics which are prone to appear at different age periods.

At the other extreme of the chart is the non-resistant host with high sensitivity, invaded by large numbers of virulent bacilli; the result is an "exudative," rapidly progressive lesion that is prone to soften, ulcerate, spread rapidly to broncho-pneumonia, pneumonia, excavation and destruction of the lung tissue. If generalization has taken place, progressive soft yellow miliary lesions of Laennec are the result. The intervening space in the chart can be filled in with many permutations and combinations of variable factors, and every type of lesion ever described may be filled in.

As an example, Aschoff's bronchogenic acinonodose lesions range from small hard clusters to large soft infiltrates, similar in that respect to the hematogenous forms. On the one hand large slowly growing tuberculomas may form, and acute pneumonic infiltrates on the other. Assman's infiltrates and Reinhardt's caseous pneumonia are examples of exudation.

Thus it is possible to give a novel and modern explanation of Virchow's "dualism," which represents the two extremes just described, without his implication of malignancy. The author's concept may be considered as Virchow's dualism modified by Laennec's unity of cause. An additional feature is that there are a host of possible intermediate types between the two extremes.

By this system the motley pattern of tuberculous lesions can be visualized and better understood. In

the final analysis they are a resultant of two widely variable interacting biological agents modified by the aging of the lesions and the mechanical factors that sometimes enter in.

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